Articles

Cost-Effective Therapy for Hypertension

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The costs of treating hypertension are out of control. The Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure and others recommend the use of diuretics and β-blockers as first-line agents. Newer drugs such as calcium channel blockers, α-blockers, and angiotensin-converting-enzyme inhibitors have improved metabolic profiles, but have not been proved in long-term, randomized, controlled trials to reduce morbidity and mortality. Our General Medicine Clinic has gradually shifted toward prescribing the newer agents. We reviewed our drug use, evaluated the literature, and made recommendations in the form of guidelines. Clinicians' concerns included quality-of-life issues, sexual dysfunction, metabolic changes—lipids, potassium, insulin resistance—and others. These concerns were addressed, and a consensus was reached. Our goal is to streamline therapy, reduce costs, and provide proven effective medication.

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The treatment of hypertension is a daily part of primary care. About 50 million Americans have hypertension. Of these, 30 to 34 million are receiving drug therapy. Total health care costs for hypertension have been estimated at $15 billion per year. Medication cost is an important cause of noncompliance. In recent years, there has been a shift from older, well-studied, and inexpensive drugs to newer and more expensive medications. In the General Medicine Clinic of the Veterans Affairs (VA) Medical Center, Ann Arbor, Michigan, we have reduced the use of diuretics and β-blockers in favor of calcium channel blockers, α_1-blockers, and angiotensin-converting-enzyme (ACE) inhibitors. The new agents have theoretical advantages, but remain unproved in terms of morbidity and mortality.

The Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC) has been providing recommendations to clinicians since 1977. During this time, there has been a steady decline in the mortality rates for stroke (57% reduction) and coronary artery disease (50% reduction).[1] Patients' awareness of hypertension, drug treatment, and adequate control has increased. Lifestyle modifications—weight loss, exercise, and moderation of dietary salt and alcohol intake—are recommended for the prevention and management of high blood pressure.

Treatment guidelines provide a means to streamline therapy, reduce costs, and provide effective medication. After discussions with clinic staff—staff physicians, nurse practitioners, physician assistants, and residents in internal medicine—we developed guidelines for hypertension therapy (Figure 1). The recommendations were evidence based. We discussed clinicians' concerns with the drugs, presented data regarding these concerns, and modified the guidelines so that a consensus was reached. This article demonstrates how local guidelines can be developed from available evidence and national guidelines and tailored to the needs and concerns of a particular community.

Guidelines of the Fifth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure

The most recent JNC report, its fifth, published in 1993, focused on the evaluation, classification, primary prevention, and drug therapy for hypertension.[1] Two major changes from previous JNC reports included a new classification system and a revised treatment algorithm. The old classification of hypertension as mild, moderate, or severe focused on the diastolic blood pressure. The new system is in stages, which incorporate both systolic and diastolic blood pressures. Accumulating data show the systolic blood pressure to be a strong predictor of cardiovascular risk.

Diuretics and β-blockers are now the preferred drugs for first-line therapy. Angiotensin-converting-enzyme inhibitors, calcium channel blockers, α_1-blockers, and α_1-β–blockers are recommended for use as alternative treatments. The JNC's fourth report included ACE inhibitors and calcium channel blockers as first-line drugs.[2] Costs were not considered, although β-blockers and diuretics are much less expensive than the other two classes of drugs. The recommendations were based on available evidence from long-term trials showing reduced morbidity and mortality with these agents. The Canadian and British hypertension societies have made similar recommendations.[3,4]

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
CHD = coronary heart disease
CI = confidence interval
COPD = chronic obstructive pulmonary disease
HDL = high-density lipoprotein
JNC = Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure
MRC = Medical Research Council
SHEP = Systolic Hypertension in the Elderly Program
VA = Veterans Affairs

In 1990 a meta-analysis of previous hypertension trials showed a 42% reduction in the incidence of stroke (95% confidence interval [CI], 33% to 50%) and a 14% reduction in the incidence of coronary heart disease (CHD) (95% CI, 4% to 22%).[5] The reduction in the incidence of stroke met expectations based on epidemiologic data of lowering diastolic blood pressures 5 to 6 mm of mercury over five years, but the CHD results fell short (expected 20% to 25% reduction). The expected CHD reduction was based on long-term (>10 years) follow-up. The relatively short duration (<5 years) of the trials may explain some of this difference. Recent studies have shown a more impressive reduction in the CHD incidence. When the results of the Systolic Hypertension in the Elderly Program (SHEP),[6] the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension),[7] and Medical Research Council (MRC)[8] trials are added to those of 14 previous trials,[9] the reduction in the incidence of CHD events is 16% (95% CI, 8% to 23%). The better results of recent trials may reflect lower doses of thiazides, the use of potassium-sparing diuretics, and potassium supplementation. A recent meta-analysis of hypertension therapy in elderly patients (aged 60 and older) showed a 12% reduction in overall mortality, a 36% reduction in stroke mortality, and a 25% reduction in CHD mortality.[10]

Drug Use

The outpatient pharmacy budget for our General Medicine Clinic in 1994 was $1.8 million. More than 30% was devoted to cardiovascular drugs. Table 1 gives a list of VA drug acquisition costs versus local pharma-

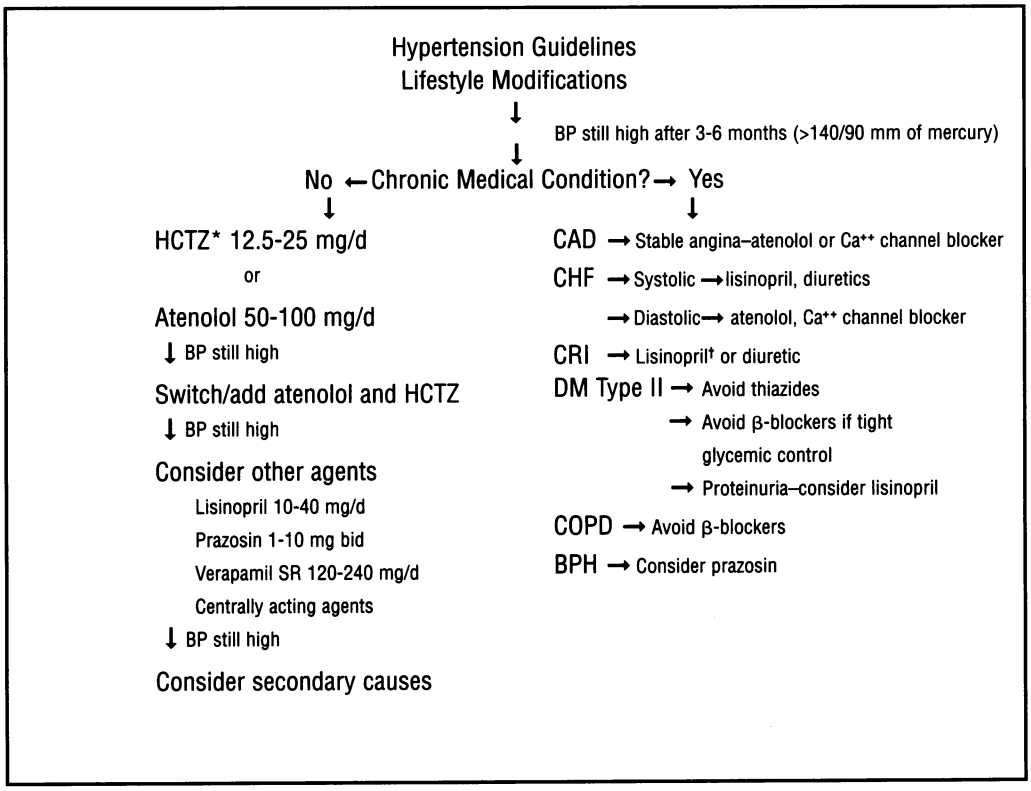

Figure 1.—Guidelines for the treatment of hypertension are outlined. These guidelines were developed for mild to moderate hypertension (essential). Patients with severe hypertension or target organ damage may require more aggressive treatment. Lifestyle modifications include weight loss, regular aerobic exercise, no added salt (2 grams of sodium), diet, and reduced alcohol intake (≤2 beers/day). *Potassium-sparing diuretics may be used as a substitute. †Use caution when starting lisinopril therapy in patients with chronic renal insufficiency (CRI) or coronary artery disease (CAD) because it may precipitate azotemia, hyperkalemia (especially with potassium-sparing diuretics or nonsteroidal anti-inflammatory drugs), or hypotension. Special situations include the use of β-blockers for migraines, or the use of α-blockers for symptomatic benign prostatic hypertrophy (BPH). bid = twice a day; BP = blood pressure; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease—emphysema, chronic bronchitis, asthma; DM = diabetes mellitus; HCTZ = hydrochlorothiazide, tid = 3 times a day

TABLE 1.—*Drug Costs Per Year at the Veterans Affairs Medical Center Versus Red Book 1995**

Agent (Trade Name)	*Veterans Affairs, $*	*Red Book AWP, $*
Hydrochlorothiazide, 25 mg/d	1.06	5.40
Hydrochlorothiazide and triamterene (Dyazide), 50/25 mg/d	21.12	137.64
Atenolol, 100 mg/d	14.08	45.41
Metoprolol tartrate (Lopressor), 100 mg bid	39.42	226.30
Propranolol HCl, long acting, 120 mg/d	199.93	323.76
Prazosin HCl, 2 mg bid	24.64	85.92
Doxazosin mesylate, 8 mg/d	196.42	351.96
Lisinopril, 20 mg/d	91.87	300.96
Captopril, 50 mg bid	44.35	860.64
Verapamil, sustained release, 240 mg/d	83.07	347.28
Diltiazem HCl, 90 mg tid	81.31	281.12
Extended release, 300 mg	495.96	767.92
Nifedipine (Procardia), Extended release, 90 mg/d	400.22	885.36
Amlodipine besylate, 10 mg/d	438.59	718.01
Clonidine HCl, 0.2 mg bid	5.63	16.20

bid = twice a day, HCl = hydrochloride, tid = 3 times a day

*The Veterans Affairs costs (March 1996) represent acquisition costs only. The Red Book (Medical Economics Data, Inc, Montvale, NJ) average wholesale price (AWP) represents recommended pharmacy charge less the drug-dispensing fee. Captopril is now generic, and its 1996 AWP will be substantially lower.

cy charges. Buying in bulk and government contracts reduce prices. As shown in the table, diuretics and β-blockers are much less expensive. Within drug classes, there are often pronounced differences in cost. Atenolol is much less expensive than metoprolol or long-acting propranolol at our institution. There were also differences between the pharmacies in relative costs. Prazosin is much cheaper than doxazosin at the VA, yet more expensive at a local pharmacy.

Cardiovascular drug use and cost are shown for January 1995 (Figures 2 and 3). Calcium channel blockers are our number one class, with most prescriptions being for diltiazem hydrochloride, amlodipine besylate, and extended-release nifedipine GITS [gastrointestinal therapeutic system]. We have had a steady increase in the prescribing of ACE inhibitors and calcium channel blockers. Prescribing patterns across the United States have changed in a similar direction. A study of temporal patterns in antihypertensive drug use among elderly patients found that patients with newly treated hypertension were half as likely to receive β-blockers or diuretics and twice as likely to receive ACE inhibitors or calcium channel blockers as patients with previously treated hypertension.[11] The Cleveland (Ohio) VA Medical Center has encountered nearly identical changes and has responded by developing guidelines.[12] From 1988 to 1992, the percentage of its budget devoted to calcium channel blockers and ACE inhibitors increased from 9.4% and 5.5% to 20.5%, and 8.9%, respectively.

Numerous factors influence clinicians' decisions on medication use, including advertising. At our facility, our most expensive and commonly used antihypertensive agents have also been those most promoted by drug representatives. They interact with staff and frequently provide lunches and books for the clinic. Conceding that there is no such thing as a "free lunch," the physician staff has recently agreed to eliminate drug representatives and drug lunches from the General Medicine Clinic.

Concerns With Guidelines

Concerns about diuretics and β-blockers need to be addressed. Many perceived side effects are not supported by the literature. These issues include quality of life, sexual dysfunction, drug effectiveness, alteration in lipids, insulin resistance, and hypokalemia.

Quality of Life

Many of the staff felt that the use of diuretics and β-blockers reduces patients' quality of life. An excellent review has been done on quality of life and hypertension.[13] Many patients with hypertension have symptoms that include headache, blurred vision, unsteadiness, sexual dysfunction, and cognitive impairment. Antihypertensive therapy generally reduces symptoms and improves patients' quality of life. Quality-of-life measures include well-being, mental health, energy, cognitive or motor function, and sexual function.

The use of methyldopa and propranolol hydrochloride worsen the quality of life. Taking propranolol may increase the risk of depression. In contrast, β_1-selective β-blockers (β_1-blockers) have effects on quality-of-life measures similar to those of calcium channel blockers and ACE inhibitors. A recent study evaluating quality of life and cognitive and motor function for hydrochlorothiazide, enalapril, and propranolol showed no impairment in cognitive or motor skills (although propranolol did reduce overall quality of life).[14] Fatigue is a common complaint before medication. No differences in the incidence of fatigue were noted between the use of β_1-blockers and that of ACE inhibitors.

The Treatment of Mild Hypertension Study compared five drug classes with placebo.[15] Quality-of-life measures improved with drug therapy, but those of only chlorthalidone and acebutolol reached significance ($P < .05$). Erectile dysfunction occurred in 16.5% of those taking placebo versus 13.1% of those on drug therapy ($P = .02$) (10.4% for acebutolol, 17.3% for chlorthalidone). The Trial of Antihypertensive Interventions and Management (TAIM) study evaluated quality of life and sexual dysfunction when taking placebo, chlorthalidone, or atenolol.[16] Both treatment groups had improved quality of life, although the chlorthalidone group had more erection problems (17% versus 7% in placebo, $P = .005$). A recent review on sexual dysfunction with antihypertensive medications concludes that sexual dysfunction at baseline is common in men with hypertension and increases with the use of diuretics.[17] Data regarding the use of propranolol are less convincing. A VA cooperative study compared six drug classes

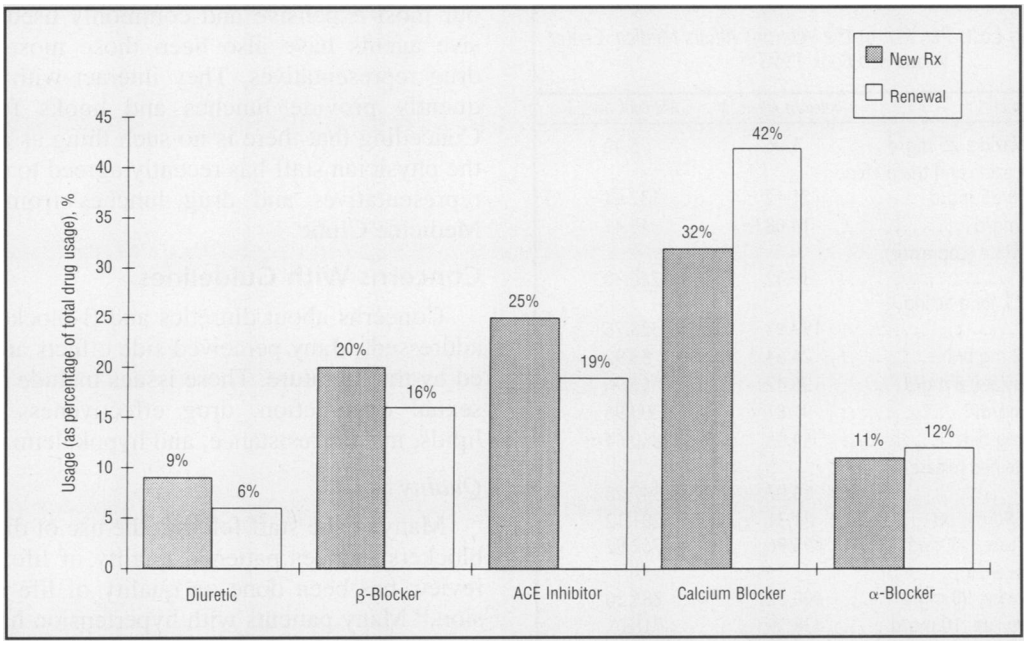

Figure 2.—The graph shows the cardiovascular drug use in general medical outpatients in January 1995. Miscellaneous drugs made up 3% of new and 5% of renewal prescriptions. ACE = angiotensin-converting enzyme

and found no differences in erectile dysfunction.[18] In this study, only clonidine and prazosin therapy were associated with increased overall side effects. Hydrochlorothiazide and atenolol had the lowest dropout rates for side effects.

Effectiveness

The newer antihypertensive drugs are often perceived as more effective. Most studies show similar blood pressure responses using different drug classes.[15,18] An individual drug adequately controls blood pressure in 40% to 60% of patients with mild to moderate hypertension. In the VA cooperative trial, African Americans responded better to the use of diltiazem (although many required the highest dose). Older patients responded well to all drug classes.

Lipids

Of our hypertensive patients, 40% to 50% have hyperlipidemia. Clinicians are often uncomfortable prescribing diuretics and β-blockers to these patients. Thiazides cause a short-term increase in total cholesterol and low-density lipoprotein levels of 5% to 7%. Long-term diuretic-based trials, however, show minimal change from the placebo group.[19] In the Treatment of Mild Hypertension Study, cholesterol levels in the group taking chlorthalidone (15 mg per day) were elevated at one year, but returned to baseline (placebo) over the four-year study.[15] β_1-Blockers may increase triglyceride levels and lower high-density lipoprotein (HDL) levels. In the Treatment of Mild Hypertension Study, the HDL levels in patients taking acebutolol remained unchanged, whereas in other groups they increased 1 to 2 mg per dl. Many staff have favored the use of α-blockers, which raise the HDL:total cholesterol ratio by 10% and decrease triglyceride levels by 10%.[20] Regimens of ACE inhibitors and calcium channel blockers have minimal effect on lipids.

The minor degree of long-term lipid changes with the use of diuretics and β-blockers is of uncertain importance. These changes would not affect management strategies in hyperlipidemia patients in most cases. Until long-term data confirm improved morbidity and mortality with the newer drugs, "soft" data (that is, metabolic variables) should not be used to make decisions on drug selection.

Insulin Resistance and Diabetes Mellitus

Diabetes mellitus is prevalent in this population. About 15% of elderly patients with hypertension have diabetes. The use of thiazides increases insulin resistance, particularly when used in high doses or causing hypokalemia. β_1-Blockers have minimal effect on insulin resistance, but can reduce the adrenergic symptoms of hypoglycemia. Calcium channel blockers are neutral. α-Blockers and, to a lesser extent, ACE inhibitors decrease insulin resistance. In most of our diabetic patients, their diabetes is controlled with diet, oral medication, or once- or twice-a-day insulin regimens. Tight control with insulin pumps or frequent injections is uncommon. In patients without frequent hypoglycemia, we have used β_1-blockers without problems.

Diuretic use is more controversial. In a cohort study, cardiovascular mortality was higher in patients with hypertension and diabetes mellitus treated with diuretics than those treated with other agents or no medication.[21]

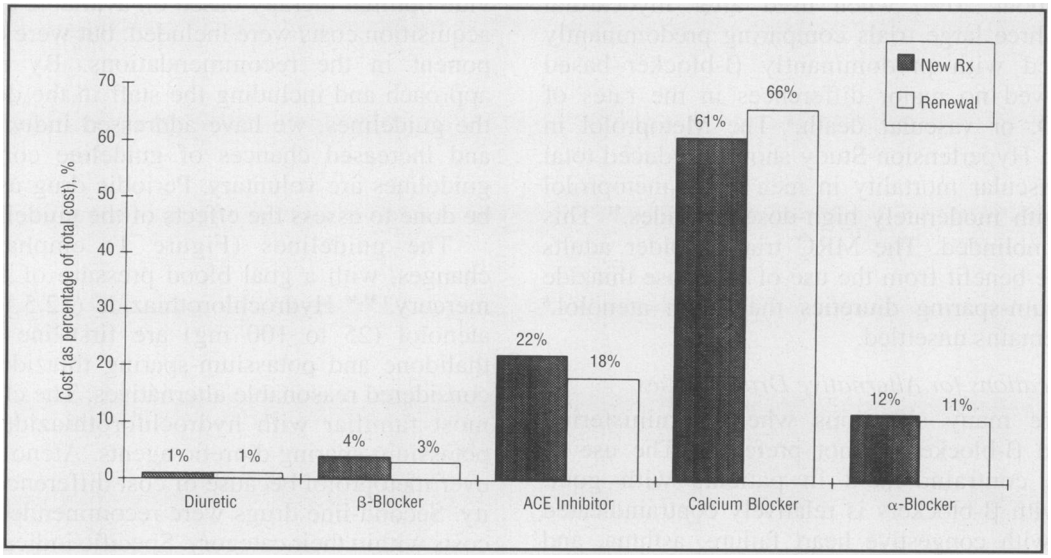

Figure 3.—The graph shows the relative cost of cardiovascular drugs in general medical outpatients in January 1995. Miscellaneous drugs made up 1% of new and of renewal prescription costs. ACE = angiotensin-converting enzyme

The type of diuretic, dose, and metabolic consequences were not given. The study's conclusions are also weakened by the lack of baseline data on target organ disease in each group. The JNC's Fifth Report and the British Hypertension Society recommend using diuretics with caution, and the Canadian Hypertension Society considers thiazides as second-line antihypertensive agents.[1,4,22] A case-control study found that thiazides did not increase the risk of diabetes therapy beyond that of other blood pressure agents.[23] Large diuretic-based trials, including SHEP and the Hypertension Detection and Follow-up Program,[24,25] have shown that the diabetic subgroup benefits from therapy similar for that for patients without diabetes.

Diabetic patients are at an increased risk for renal disease. Administering ACE inhibitors and some calcium channel blockers (non-dihydropyridine) slows the progression of diabetic renal disease (glomerular filtration rate decline and albuminuria).[26] Many staff thought we should give all diabetic patients ACE inhibitors to reduce the risk of renal disease. Their use in diabetic patients with normal urinary albumin concentrations to delay renal disease, however, remains unproved. One study compared the use of captopril with conventional therapy in hypertensive patients with diabetes type II.[27] Blood pressure responses were similar. In patients with microalbuminuria, urinary albumin excretion improved with captopril use more than with conventional therapy. In diabetic patients with normal albumin concentrations, there was no difference. Renal function remained the same in both treatment groups over the 36-month study.

Hypokalemia

Hypokalemia is a major concern with thiazides. A dose-response curve between nonpotassium-sparing diuretics and serum potassium levels exists.[28] Data on serum magnesium and intracellular magnesium-potassium levels are sparse. A case-control study concluded that high-dose thiazide therapy is associated with an increased risk of sudden cardiac death.[29] The combined use of low-dose thiazide and potassium-sparing agents was associated with the lowest risk. This may explain the better CHD results in recent trials,[6-8] which used lower doses of diuretics. The MRC trial participants receiving low-dose thiazide with a potassium-sparing agent had a 40% reduction in CHD mortality.[8] High-dose thiazides may partially explain the inability of older hypertension trials to achieve the expected reduction in CHD mortality.

Our staff is in general agreement on the use of high-dose thiazides. If patients do not respond to a regimen of low-dose hydrochlorothiazide (12.5 to 25 mg) plus or minus potassium-sparing agents, then other drugs are tried or added.

Left Ventricular Hypertrophy

Left ventricular hypertrophy is common in hypertensive patients (30% by echocardiogram) and increases with severity and age. Many clinicians thought that certain drug classes were superior in this group, including β-blockers, calcium channel blockers, and ACE inhibitors. A recent review of hypertension and the heart found that all antihypertensive agents are effective in reducing left ventricular hypertrophy (exceptions include minoxidol and hydralazine).[30] Some drug classes reduce left ventricular mass more rapidly. In the Treatment of Mild Hypertension Study, all drug classes reduced left ventricular hypertrophy, with the largest reduction in the group on chlorthalidone therapy.[15]

β-Blockers Versus Diuretics

Of the preferred drugs—β-blockers or diuretics—is one better? We might expect β-blockers to be more effective in reducing CHD mortality. They reduce

mortality (about 20%) when used after myocardial infarction. Three large trials comparing predominantly diuretic-based with predominantly β-blocker–based therapy showed no major differences in the rates of stroke, CHD, or vascular death.[5] The Metoprolol in Patients with Hypertension Study showed reduced total and cardiovascular mortality in men using metoprolol compared with moderately high-dose thiazides.[31] This study was unblinded. The MRC trial in older adults showed more benefit from the use of low-dose thiazide plus potassium-sparing diuretics than with atenolol.[8] This issue remains unsettled.

Specific Indications for Alternative Drug Classes

There are many situations where administering diuretics and β-blockers is not preferred. The use of thiazides is contraindicated in patients with gout. Treatment with β-blockers is relatively contraindicated in patients with congestive heart failure, asthma, and symptomatic chronic obstructive pulmonary disease (COPD). Patients with evidence of mild COPD may tolerate taking β_1-blockers. Symptoms of benign prostatic hypertrophy may respond to the use of α-blockers. Angiotensin-converting-enzyme inhibitors are first-line agents for the treatment of congestive heart failure. Morbidity and mortality in patients with coronary artery disease and myocardial infarction have improved with the use of β-blockers, calcium channel blockers, and ACE inhibitors. The use of ACE inhibitors may slow the progression of chronic renal insufficiency more than other antihypertensive agents.[32]

Cost Containment

Cost containment is a growing concern. The cost per year of life saved from treating mild to moderate hypertension has been estimated at $40,000 for younger adults and less in older adults. These costs compare well with other preventive strategies. A computer simulation on costs for treating patients (aged 35 to 64, with diastolic blood pressures >95 mm of mercury and no known coronary artery disease) calculated the costs per year of life saved with various monotherapies.[33] The results were $10,900 for propranolol, $16,400 for hydrochlorothiazide, $31,600 for nifedipine, $61,900 for prazosin, and $72,100 for captopril. Studies of this type, however, must make numerous assumptions using models and methods of cost-effective analysis that may be based on insufficient data.

A retrospective study of drug costs looked at total costs of treating hypertension with various regimens.[34] These costs included those for acquisition, supplemental drugs, laboratory tests, clinic visits, and complications. The costs per year of treatment were $895 for β-blockers, $1,043 for diuretics, $1,165 for α_2-agonists, $1,243 for ACE inhibitors, $1,288 for α-blockers, and $1,425 for calcium channel blockers.

Summary

The purpose of this review was to evaluate our antihypertensive drug use and to develop guidelines to provide optimal therapy based on available evidence. Drug acquisition costs were included, but were only one component in the recommendations. By using a team approach and including the staff in the development of the guidelines, we have addressed individual concerns and increased chances of guideline compliance. The guidelines are voluntary. Periodic drug use studies will be done to assess the effects of the guidelines.

The guidelines (Figure 1) emphasize lifestyle changes, with a goal blood pressure of 140/90 mm of mercury.[1,35,36] Hydrochlorothiazide (12.5 to 25 mg) and atenolol (25 to 100 mg) are first-line drugs. Chlorthalidone and potassium-sparing thiazide diuretics are considered reasonable alternatives. The clinic staff were most familiar with hydrochlorothiazide in the non–potassium-sparing diuretic agents. Atenolol was chosen over metoprolol because of cost differences at our facility. Second-line drugs were recommended based on the costs within their category. Specific indications for alternative antihypertensive agents in coexisting medical problems were addressed.

After five months of guideline use, several changes have been noted. The number of calcium channel blocker prescriptions has decreased 34%. The use of ACE inhibitors has not changed. The number of prescriptions for thiazides, β-blockers, and α-blockers increased 37%, 51%, and 43%, respectively. Our total number of prescriptions for these agents has increased, without a substantial change in our population base. We attribute this change to more aggressive blood pressure treatment. Our current drug costs are 18% lower than six months before. We anticipate more change as staff members become more comfortable with the guidelines. The clinic staff has generally had positive responses to the guidelines. One problem area has been taking patients off their regimens of ACE inhibitors or calcium channel blockers, which have previously been first-line drugs or monotherapy. Many of these patients feel well and have good blood pressure control. Clinicians feel uncomfortable switching them to guideline-based therapy (diuretic or β-blocker). My experience has been that most patients are open to change when the guidelines are explained.

We are fortunate to have the opportunity to improve care and reduce costs simultaneously. In the next five to ten years, there will be long-term, randomized, controlled trials evaluating the newer agents. Whether their improved metabolic profiles result in better morbidity and mortality over diuretics and β-blockers remains to be proved.

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